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CMR Workshop Series

Long-Term Animal Studies

Their Predictive Value for Man

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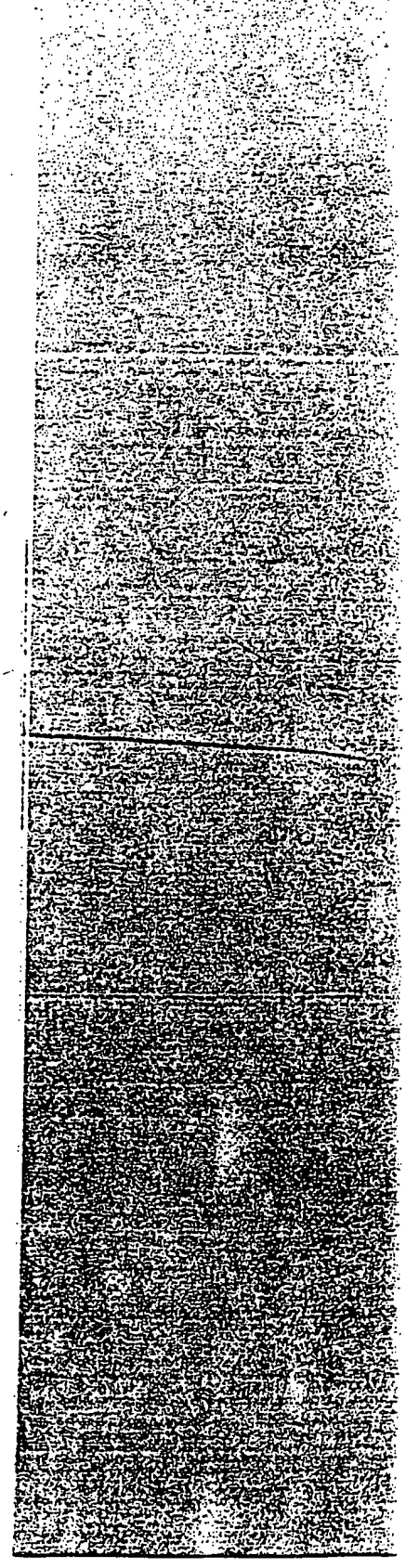

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1.3 What is expected from repeated-dose studies by clinical pharmacologists

Professor M. D. Rawlins

The expectations of clinical pharmacologists from repeated-dose studies vary with the type of investigation or uses with which they are concerned. In Phase I studies, the principal objective is to investigate a new compound's human pharmacology and pharmacokinetics by administering single doses or intravenous infusions of short duration. By contrast, Phase II and III studies are concerned with investigating therapeutic efficacy and safety in placebo or comparative trials. Finally, Phase IV studies, performed after a drug has been licenced for general use, aim to investigate further therapeutic applications and to assess safety in a wider and larger patient population. In designing and performing these different studies, clinical pharmacologists draw on the full range of 'preclinical' investigations and the relevance of repeat-dose studies is examined from this perspective.

PROBLEMS DURING STUDIES WITH NEW DRUGS

Clinical pharmacologists have three interrelated anxieties when designing and undertaking studies with new drugs. First, clinical pharmacologists wish to avoid harming either their volunteers or their patients. Since the object of Phase I studies, however, is to produce measurable physiological or biochemical changes in the subjects, some risk is inevitable. Second, clinical pharmacologists must select appropriate doses. On the one hand, they will wish to avoid using 'no effect' doses since this will invalidate the purpose of the investigation; and on the other hand, they will seek to avoid administering doses that are likely to be hazardous.

Third, clinical pharmacologists will invariably wish to construct a

protocol which allows them to study the drug's important human pharmacological and pharmacokinetic properties for an adequate period of time. Since it is impossible, in a single study, to investigate all the conceivable pharmacological action of a drug, clinical pharmacologists draw heavily on the results of preclinical studies in deciding which pharmacodynamic and pharmacokinetic observations to make. Although initial pilot 'tolerance' studies in volunteers or patients may provide some help in designing adequate protocols, they are unlikely to provide more than minimal information.

THE VALUE OF PRECLINICAL STUDIES IN CLINICAL PHARMACOLOGICAL INVESTIGATIONS

Preclinical studies (Table 7) play a major role in the clinical pharmacological evaluation of new compounds.

Table 7 Preclinical studies available to clinical pharmacologists

1. Animal pharmacology	
	– *in vitro*
	– *in vivo*
2. Animal pharmacokinetics and metabolism	
3. Acute toxicity tests	
4. Short-term mutagenicity tests	
5. Repeat dose toxicity tests	
	– subacute and chronic toxicity
	– reproductive toxicity
	– carcinogenicity

Animal pharmacological studies provide crucial information about possible interactions between a new compound and a variety of tissues and organs. Quantitative *in vitro* pharmacological studies of different receptor sites will enable some assessment to be made of effects likely to be observed *in vivo*. *In vivo* animal pharmacological studies complement *in vitro* investigations, and extend knowledge of a drug, particularly with respect to its likely overall effects on the cardiovascular, respiratory and central nervous systems.

The information provided by animal pharmacology tests is the most important part of the preclinical programme in establishing whether it is safe to proceed to Phase I studies, the dosages that may safely be employed, and the pharmacological actions that should be examined most closely. They are also of value to clinical pharmacologists during the design and conduct of Phase II studies, although by this stage the results of properly conducted human pharmacological investigations should be available.

Studies of a new drug's *pharmacokinetics* in animals, despite inter-

species differences in routes and rate of elimination, are of some value in providing information about the likely overall fate of a compound in man and its possible duration of action[1].

More importantly, they can contribute to better assessment of the significance of any abnormalities detected during repeat dose toxicity studies. Thus, they make a useful contribution to the design and performance of Phase I studies, and are of special value in Phases II and III (see below).

The value and significance of *short-term mutagenicity tests* have been extensively reviewed elsewhere[2-4]. For the purposes of the present discussion, it is sufficient to say that clinical pharmacologists would not wish to administer a known mutagen to volunteers as part of a Phase I study, and would only consider giving mutagens to patients in special circumstances (e.g. those with life-threatening malignancy).

Acute toxicity studies, with a numerical result expressed as the median lethan dose (LD50) or minimal lethal dose (MLD), have only a very limited role in assessing the likely toxicity of a compound for man. They do, however, provide some basis for establishing the upper likely limit of tolerance, and whilst I am sympathetic to suggestions[5,6] for the adoption of simplified protocols, I would not wish to see such studies abandoned altogether.

Repeat dose toxicity tests, designed to reveal the general toxicology of the compound during chronic administration, have several objectives. First, in conjunction with appropriate animal pharmacokinetics, they provide some information about the possible hazards and risks to be encountered in man. Second, they give an indication of the likely target organs, which should therefore undergo special monitoring for toxicity during Phases II and III. Third, they offer some guidance in distinguishing adverse drug reactions from intercurrent disease both during clinical trials, and once a drug is marketed. Such studies are therefore of considerable value in the design and conduct of Phase II and III studies, but have only limited value in Phase I Studies. It is for this reason that regulatory guidelines in the UK[7] require only 14 day repeat dose toxicity studies in animals (including general and gonadal histology) before administration of single doses of new agents to a patient.

LIMITATIONS OF PRECLINICAL STUDIES FOR CLINICAL PHARMACOLOGISTS

The majority of adverse drug reactions encountered in clinical practice are dose-dependent, Type A effects, which are usually predictable from animal pharmacological and toxicological investigations[8,9]. However, although pre-clinical studies may reveal potential hazards for man, they are less satisfactory in making quantitative predictions about their likely incidence.

6–9 months after renal transplantation is shown in Figure 1. The manufacturer's dosage recommendations were strictly followed for the initiation of treatment, but dosages were thereafter adjusted to maintain a trough plasma concentration around 100–200 ng ml^{-1}. The problems encountered in achieving this during routine clinical care are clear in Figure 1; they are due to intra- and interindividual pharmacokinetic differences, as well as possibly to poor compliance and drug–drug interactions. Thus, the wide variation in plasma cyclosporin concentration observed under conditions of ordinary clinical use may further confound the attempt to assess risk purely from preclinical studies.

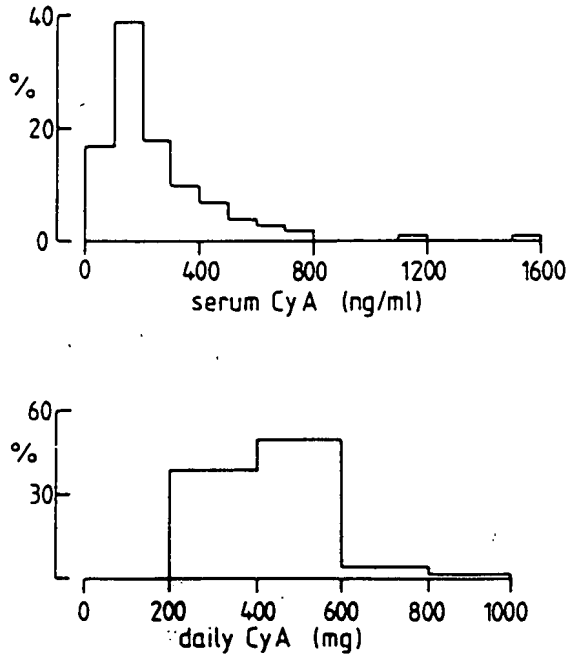

Figure 1 Distribution of 'trough' serum cyclosporin concentrations (above) and dosages (below) amongst six patients receiving the drug after renal transplantation.

CONCLUSIONS

Clinical pharmacologists draw on the full range of preclinical investigations when designing and executing studies in man. Their relative importance depends on the type of study but, considered together, although they are sufficiently robust to identify many potential hazards for man they are less